COBE BCT

COBE BCT, Inc.
Blood Component Technology
A Gambro Company

March 17, 1999

Documents Management Branch (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 98D-0545
"Guidance for Industry. Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods"

Dear Sirs;

Last Fall we submitted comments on the Guideline referenced above published in the Federal Register concerning the collection of packed red blood cell units using an automated apheresis system. Recently a very good review paper was published in the February 1999 blood banking journal Transfusion that described the risks and benefits of collecting 2 units of red blood cells by apheresis (Shi PA and Ness PM. Two-unit red cell apheresis and its potential advantages over traditional whole-blood donation. Transfusion. 39:218 - 225, see attached) The Shi and Ness paper referenced the FDA draft guidelines for collecting red cells and the recommendations from the Haemonetics Corporation for double red blood cell units collected using the MCS+.

In reading this paper I discovered interesting differences when I compared the criteria used with the COBE Trima for including or excluding donors who could donate 2 red blood cell units to those guidelines recommended by Haemonetics. The COBE Trima guidelines are more conservative for smaller male donors, and less conservative with larger female donors. This dichotomy reinforces the problem we described in our original comments concerning the FDA guidelines, and shows the weakness in trying to exclude donors based on sex, weight, and pre hematocrit. That is, we feel that it makes more sense to set a post donation hematocrit standard for the donors who donate red blood cells by apheresis, rather than trying to bracket the body size of potential donors in an attempt to eliminate donors whose post hematocrit will be too low.

By taking the minimum requirements for a whole blood donor (female, 5' 1", 110 lbs., 38 Hct) and using the Nadler Allen equation to predict total blood volume, the post hematocrit following the collection of a 450 mL unit of blood would be approximately 32. This is the basis for our current recommended post hematocrit of 32 following the collection of a red cell units using the COBE Trima System. According to our calculations, the post hematocrit can be as low as 30 for the red cell donors described in Table 3 of the Shi and Ness paper. This

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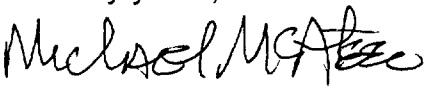
means that the two apheresis systems currently available in the United States for the collection of red blood cell units exclude donors using different criteria, which could lead to confusion. If FDA is comfortable with a minimum post donation hematocrit of 30, we can adjust our recommendations, and implement that change in the COBE Trima software. If not, the Haemonetics recommendations will need to be to be reassessed.

We appreciate the opportunity to continue to review and respond to the draft guideline document. Please contact me with any questions at 303-231-4112 or 800-525-2623 extension 4112. I can also be reached by E-Mail at mike.mcateer@cobe.com.

Sincerely yours;



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enclosure

Two-unit red cell apheresis and its potential advantages over traditional whole-blood donation

P.A. Shi and P.M. Ness

This article discusses the risks and benefits of the 2-unit red cell (RBC) apheresis procedure. Unlike traditional whole-blood collection, apheresis allows desired component(s) to be selectively retained, with the unwanted components returned to the donor. Maximizing the collection of a selected component, however, must be balanced by consideration of the health risk to the donor. For example, plateletpheresis, though it may decrease the platelet count to less than a normal level of 150,000 per μL, has become a routine procedure among blood centers because platelet counts may fall below normal levels without significant risk of bleeding, and they usually return to preapheresis levels within 4 days.[1]

Although the apheresis of 1 unit of RBCs with 2 units of fresh-frozen plasma has been Food and Drug Administration (FDA)-approved since October 1995, approval for 2-unit RBC apheresis is more recent, as preliminary studies were needed to define donor criteria that would prevent the precipitation of symptomatic anemia. Following these studies, autologous 2-unit RBC apheresis received FDA approval in April 1996 and allogeneic 2-unit RBC apheresis did so in April 1997.

The only 2-unit RBC apheresis instrument granted premarket clearance by the FDA was the MCS+ (LN 8150, Haemonetics Corp., Braintree, MA), and therefore the preliminary studies leading to FDA approval for the 2-unit RBC apheresis procedure used this device. This use of this instrument will therefore be described in detail.

ABBREVIATIONS: AABB = American Association of Blood Banks; AS-3 = additive solution 3; FDA = Food and Drug Administration; Hb = hemoglobin; Hct = hematocrit; RBC(s) = red cell(s); VO_2 max = maximal O_2 consumption.

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The MCS+

The MCS+ (Fig. 1) is designed to collect RBC units on the basis of absolute RBC volume, with the term "absolute" meaning a hematocrit (Hct) of 100 percent. The programmable absolute RBC volume ranges from 90 to 210 mL per unit, with a standard deviation in practice of ≤6 percent.[2] This ability to collect a specified absolute RBC volume represents a significant advantage over traditional whole-blood collection, in which the absolute RBC volume collected varies widely, depending on donor Hct and blood volume. For example, if an absolute RBC volume of 180 mL is programmed, the absolute RBC volume collected may vary from 169 to 191 mL (± 6% of the 180-mL setting). In contrast, by an estimation that traditional whole-blood collection volumes range from 405 to 495 mL and donor Hcts from 38 to 54 percent, the absolute RBC volume of an RBC unit collected by traditional whole-blood donation may vary from 154 to 267 mL.

With each procedure, a single-use, sterile, disposable set is installed into the MCS+ and, the set is primed. Three types of disposable sets are available: with CP2D and additive solution 3 (AS-3) already attached (Haemonetics); with CP2D and AS-3 luer connectors only (Haemonetics); and with a spike attached for CPDA-1 (Haemonetics). The latter two "dry" disposable sets have longer shelf-lives because they replace preconnected solution with bacteriostatic filters for solution connection at the time of donation. The attached CP2D and AS-3 set is shown (Fig. 2). The blow-molded bowl is the same in all three sets, and its function is shown in Fig. 3.

The desired cuff pressure, RBC volume for RBC Bag 1, RBC volume for Bag 2, saline return volume, and draw and return speeds of the pump are selected. After a single-site venipuncture with the 18-gauge needle already connected to the diposable set, the 2 units of RBCs are collected in two cycles, with each cycle consisting of draw, transfer, and return phases. The procedure with the attached CP2D and AS-3 disposable set is described.

In the draw phase, whole blood withdrawn at a rate of 20 to 100 mL per minute mixes with CP2D metered at a ratio of 1 part of CP2D to 15 parts of whole blood. This anti-

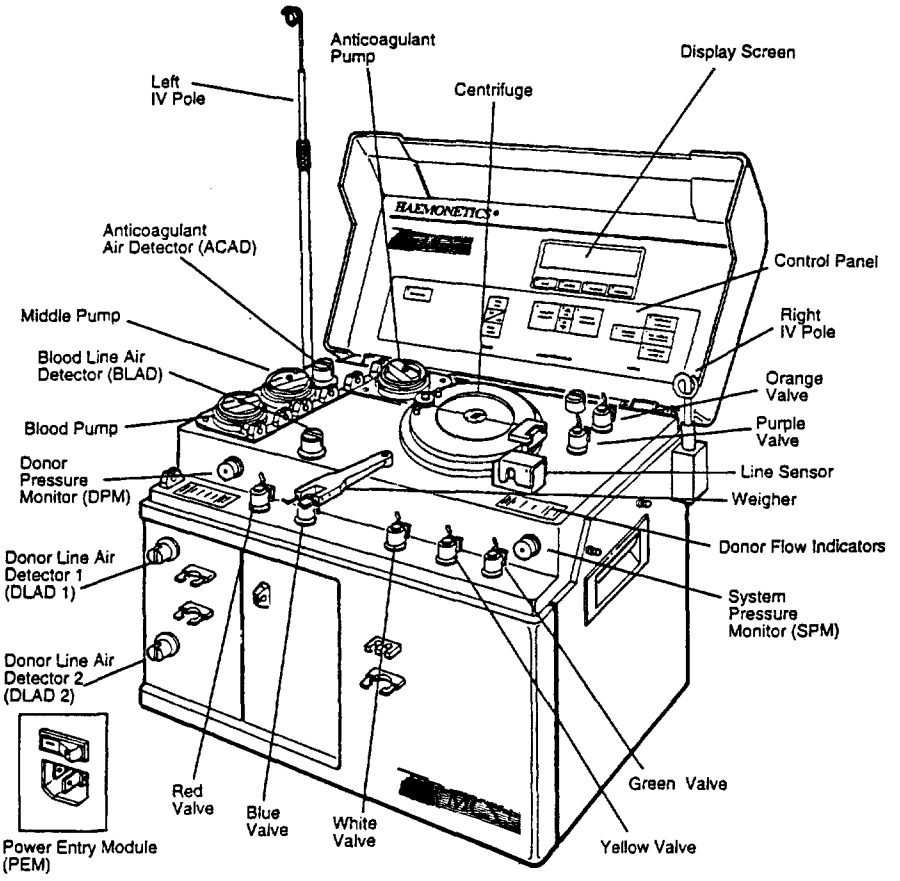

Fig. 1. The MCS+ (IV = intravenous).

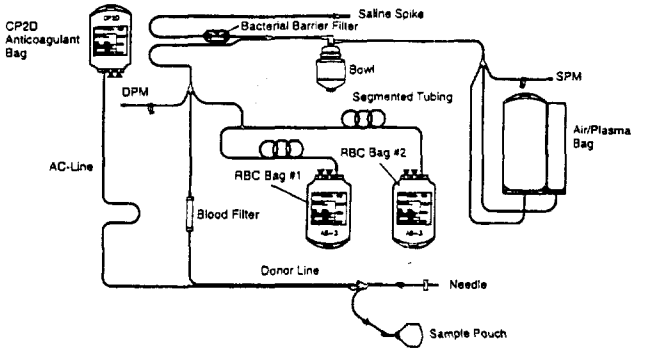

Fig. 2. Two-unit RBC CP2D and AS-3 disposable set (AC = anticoagulant; DPM = donor pressure monitor; SPM = system pressure monitor),

coagulated blood is pumped into the centrifuge bowl, which is spinning at 7000 rpm to separate the plasma from the RBCs. The plasma is diverted into the plasma bag while RBCs packed at a Hct of 84 percent remain in the bowl. Once the bowl completely fills to a volume of 250 mL with RBCs packed at an 84-percent Hct, the MCS+ stops drawing blood and stops the centrifuge. The transfer phase is then initiated.

In the transfer phase, the programmed absolute RBC volume is routed from the bowl into one of the RBC bags filled with 100 mL of AS-3. For example, if the target absolute RBC volume is 180 mL, then 214 mL of the 250 mL of packed RBCs (Hct, 84%) in the bowl is transferred into the RBC bag. Once the target absolute RBC volume has been transferred into the RBC bag, the return phase is initiated. In the return phase, plasma from the plasma bag is returned to the donor through the bowl with any excess RBCs in the bowl and half of the normal saline return, which has a programmable range of 130 to 750 mL.

This entire cycle is simply repeated to collect the second RBC unit, and a final rinse with part of the programmed saline return volume through the disposable set reduces the absolute volume of RBCs wasted in the equipment tubing to about 5 to 10 mL. The volume of anticoagulant in the RBC units collected with AS-3 is approximately 5 mL of CP2D, and that collected with CPDA-1 is approximately 35 mL CPDA-1.[3] An issue

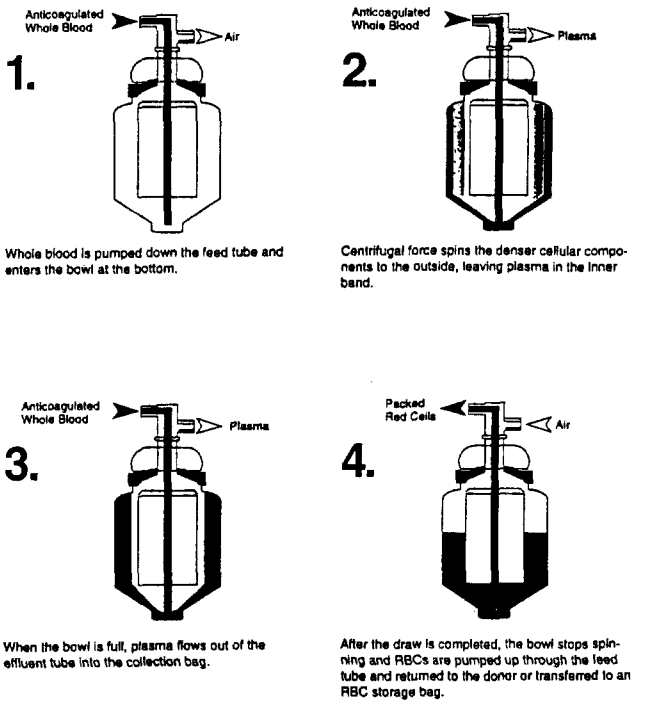

Fig. 3. How the bowl works.

of clinical concern with this procedure is that the total extracorporeal volume drawn into the apheresis machine for the collection of each unit varies inversely with the Hct of the donor (Table 1), with the maximum volume being 571 mL in a donor with a Hct of 36 percent. For comparison, the standards of the American Association of Blood Banks (AABB) allow whole-blood donors to donate up to 525 mL of whole blood or up to 15 percent of their estimated whole-blood volume.[5]

The typical time required for the 2-unit RBC apheresis procedure is 45 to 60 minutes, and it varies depending on the programmed saline return volume, draw speed, and return speed. In contrast, the typical collection time for standard 1-unit whole-blood donation is 10 to 15 minutes.[4]

FDA guidelines for 2-unit RBC apheresis

For traditional allogeneic whole-blood donation, the AABB requires a minimum Hct of 38 percent or hemoglobin (Hb) of 12.5 g per dL, with a minimum of 56 days between donations.[5] As would be expected, FDA criteria for allogeneic 2-unit RBC apheresis donation are more stringent. For both sexes, a minimum Hct of 40 percent or Hb of 13.3 g per dL is required, and the minimum time between donation is 112 days. In addition, males should meet a minimum height and weight of 5'1" and 130 lb and females a minimum height and weight of 5'5" and 150 lb.[3] These recommendations were based on studies of approximately 600 donors who met or may even have been below the FDA criteria for allogeneic 2-unit RBC apheresis, and yet had no serious adverse clinical events.[4,6]

Strict donor criteria for traditional autologous blood collection have not been specified by the FDA, but the standards of the AABB list "suitable" guidelines to be a minimum Hb of 11 g per dL or Hct of 33 percent.[5] Similarly, the FDA has not specified absolute criteria for autologous 2-unit RBC apheresis, but recommends a minimum Hb of 12 g per dL or Hct of 36 percent and a minimum weight of 130 lb.[3] Safe-donor criteria in autologous donors need further study, however: in two of the three autologous 2-unit RBC apheresis studies, the average starting Hct was 42 to 44 percent,[2,7] and in the other study, the minimum Hct required for entry into the study was 40 percent[8] (Table 2). Therefore, even though over 1000 two-unit RBC apheresis procedures have been performed in autologous donors, it is unclear whether those donors with a starting Hct of 36 to 39 percent would safely tolerate 2-unit RBC apheresis, especially because only one of the smaller studies published data on the age of the autologous donors, and those mean ages, 55 for men and 42 for women, were relatively young.[7]

The relevance of Hct

The MCS+ operations manual contains recommendations for maximum target absolute RBC volumes for 2-unit RBC apheresis that are in accordance with FDA guidelines and are based in allogeneic donors on weight and sex (Table 3) and in autologous donors on Hct as well (Table 4). As is evident from the tables, the range of RBC volume removed from the donor (380-500 mL) is comparable to that with traditional whole-blood donation (405-495 mL), and the percentage of total blood volume removed in 2-unit RBC

TABLE 1. Estimated extracorporeal volume* per pass in 2-unit RBC apheresis

	ECV Pass 1	ECV Pass 2					
Donor	All	Male donors			Female donors		
Hct (%)	donors	130-149 lb	150-174 lb	≥175 lb	130-149 lb	150-174 lb	≥175 lb
36	571	517	542	567	493	517	542
37	556	503	527	552	478	503	527
38	542	489	514	538	464	489	514
39	529	476	501	525	451	476	501
40	517	488	513	537	464	488	513
41	505	476	501	526	452	476	501
42	494	465	490	514	441	465	490
43	483	454	479	504	430	454	479
44	473	444	469	493	420	444	469
45	463	434	459	484	410	434	459
46	454	425	450	474	400	425	450
47	445	416	441	465	392	416	441
48	436	408	432	457	383	408	432
49	428	399	424	449	375	399	424
50	420	391	416	441	367	391	416
51	412	384	408	433	359	384	408
52	405	377	401	426	352	377	401
53	398	369	394	419	345	369	394
54	391	363	387	412	338	363	387
55	385	356	381	405	332	356	381

* Estimated extracorporeal volume (ECV) presented in this table includes the collected component(s). The ECV presented in this table assumes that the RBCs collected are packed to a Hct of 84 percent, that the anticoagulant:whole blood ratio is 1:16, that the harness volume is 35 mL, that the saline infusion volume is 250 mL per pass, that the volume of packed RBCs in the full bowl is 250 mL, and that the maximum allowable RBC component is collected in Pass 1.

Table 2. Starting Hb or Hct values in autologous 2-unit RBC apheresis studies*

Study	Number of procedures	Hb (g/dL) [SD]	Hct (%) [SD]
Schmidt et al.[7]	53	14.1 [1.3]	42 [3.5]
Smith and Gilcher[2]	1052		44
Axelrod et al.[8]	43		40

* Reported as mean [+ SD] in the study by Schmidt et al., as mean in the study by Smith and Gilcher; the Hct was ≥40% in all donors in the study by Axelrod et al.

Table 3. Manufacturer's recommmendations for maximum target absolute RBC volume for allogeneic donors based on donor weight and sex

Weight	Sex	Absolute RBC volume	RBC volume*	Percentage of TBV†
130-149 lb	Male	320 mL	380 mL	8.7
	Female	Donation not recommended		
150-174 lb	Male	400 mL	476 mL	10.1
	Female	360 mL	429 mL	10.3
≥175 lb	Male	420 mL	500 mL	9.9
	Female	400 mL	476 mL	10.5

* RBC volume refers to the actual volume removed from the donor, which is higher than the absolute RBC volume because the RBCs collected in the bowl have a Hct of 84 percent.

† The percentage of total body volume (TBV) removed was estimated using the RBC volume value in the numerator (normal saline replacement was excluded from the calculation). Body surface area[9] was calculated using the FDA-recommended minimum height requirements for each sex for 2-unit RBC apheresis and the minimum weight in each weight category and then multiplying by 2740 mL per m^2 for males and 2370 mL per m^2 for females.[10]

↑ sizes, Hct, ↑ RBC volume

Table 4. Manufacturer's recommendations for maximum target absolute RBC volume for autologous donors based on donor weight, sex, and Hct

Weight (lb)	Sex	Absolute RBC volume Hct (36-39%)	Absolute RBC volume Hct (≥40%)	RBC volume for Hct ≥40%*	Percentage of TBV†
130-149	Male	320 mL	360 mL	428 mL	9.8
	Female	280 mL	320 mL	380 mL	9.8
150-174	Male	360 mL	400 mL	476 mL	10.1
	Female	320 mL	360 mL	429 mL	10.3
≥175	Male	400 mL	420 mL	500 mL	9.9
	Female	360 mL	400 mL	476 mL	10.5

* RBC volume refers to the actual volume removed from the donor, which is higher than the absolute RBC volume because the RBCs collected in the bowl have a Hct of 84 percent.

† The percentage of total body volume (TBV) removed was estimated using the RBC volume value in the numerator (normal saline replacement was excluded from the calculation). Body surface area[9] was calculated using the FDA-recommended minimum height requirements for each sex for 2-unit RBC apheresis and the minimum weight in each weight category and then multiplying by 2740 mL per m^2 for males and 2370 mL per m^2 for females.[10]

apheresis (8.7-10.5%) is less than the 15-percent total blood volume allowed by the AABB in traditional blood donation.[5] Clearly, then, the volume removed from 2-unit RBC apheresis donors is not excessive compared to that removed from traditional whole-blood donors.

Attention to the safety of 2-unit RBC apheresis can therefore be focused on whether the drop in Hb or Hct provides adequate O_2 delivery to prevent symptomatic anemia. That the Hb or Hct is an important determinant of O_2 supply to tissues is evident from the equation O_2 supply = cardiac output × [(Hb × 1.39 × %O_2 saturation) + (pO_2 × 0.003)].

Three studies of 2-unit RBC apheresis, where 400 to 500 mL of normal saline replacement was given with the procedure, found that the observed drop in the Hb or Hct of donors weighing at least 125 lb approximated that expected (Table 5). This finding immediately after apheresis[2,7] is not surprising, as the amount of normal saline replacement approximated the RBC volume removed from the donors. More important, however, the observed drop in Hb after physiologic volume equilibration, that is, 24 to 48 hours after apheresis, also matched the expected drop.[11] These data are helpful in confirming that the Hb does not fall lower than expected, and they also suggest that compensatory reticulocytosis is not yet evident at 24 to 48 hours after apheresis.

Finally, it is important to note that separate analysis by donor sex of the observed Hb drop after apheresis showed the average to be 13.6 ± 5.6 percent in men but significantly higher in women at 21.3 ± 4.4 percent (overall average Hb drop, 17.4%).[9] This difference is expected, given the smaller average blood volume of women compared to men, and the manufacturer's recommendations for maximum absolute RBC volume based on sex (Tables 3 and 4) reflect this important difference.

Symptoms reported with 2-unit RBC apheresis

Keeping in mind that most of the donors in the autologous 2-unit RBC apheresis studies had a Hct ≥40 percent, they do not appear to have more serious symptoms than traditional whole-blood donors. In the largest study of autologous donors (1052 procedures),[2] although no information is given on the nature of the reactions or the age and physical health of the donors, the reaction rate was relatively low, 0.85 percent. Axelrod et al.[11] found no significant difference in symptoms in 2-unit RBC apheresis donors (n = 43) and 43 whole-blood donors matched by age, sex, donation experience, and surgery category (Table 6). There were no

Table 5. Observed and expected drop in Hb or Hct based on absolute RBC volume removed*

Study	Absolute RBC volume removed	Preapheresis Hb (g/dL) or Hct (%) [SD]	Postapheresis Hb (g/dL) or Hct (%) [SD]	Observed drop	Expected drop
Schmidt et al.[7]	320 mL	Hb 14.1 [1.3]	Hb 11.4 [1.4]†	2.7 g/dL	2.6 g/dL
Smith and Gilcher[2]	360 mL	Hct 44%	Hct 35%	9%	9%
Smith et al.[11]	407±16 mL	Hb15.2 [1.4]†	Hb 12.5 [1.7]†	2.7 g/dL	3.0 g/dL

* Expected drop calculated by using 1) a total blood volume of 4136 mL in a 130-lb person in the studies by Schmidt et al. and Smith and Gilcher and a total blood volume of 4538 mL in the study by Smith et al., and by using 2) the estimation that an absolute RBC volume loss of 1 mL reduces the Hb by 0.34 g.

† Results reported as mean [± SD].

Table 6. Symptoms in autologous 2-unit RBC apheresis and whole-blood donors

Symptom	Number (%) of apheresis donors with symptom (n = 43)	Number (%) of whole-blood donors with symptom (n = 43)
Bruising	13 (30)	10 (23)
Pain	5 (12)	6 (14)
Tiredness	19 (44)	13 (30)
Lightheadedness	10 (23)	15 (35)
Faintness	0	0
Nausea	2 (5)	2 (5)
Shortness of breath	0	0
Other	3 (7)	2 (5)

moderate or severe reactions in the study by Schmidt et al.[7] which included autologous donors with a history of myocardial infarction, type II diabetes mellitus, hypertension requiring antihypertensive therapy, and asthma, although no numbers were specified.

Allogeneic blood donors also do not appear to have symptomatic anemia. Meyer et al.,[4] studying 40 allogeneic blood donors divided between 2-unit RBC apheresis donors and 1-unit whole blood donors over a 1-year period, found that the apheresis donors took 1 to 2 days longer than whole-blood donors to regain their baseline sense of well-being (see Table 2[4]), but only one donor in each group failed to complete the study period because of excessive fatigue. In the study by Sherman et al.[12] of eight donors (4 male, 4 female) who also underwent 2-unit RBC apheresis, only one donor (male) noted any subjective change in physical ability or work capacity (decreased exercise capacity for the first 2 weeks after the 2-unit donation) compared to his experience after traditional whole-blood donation, but he had a strenous regular exercise routine.

The most common reactions, actually, were immediate and probably attributable to citrate toxicity, rather than symptoms specific to RBC removal (Table 7). Meyer et al.[4] noted chest tightness during eight apheresis collections and hypotension during three collections from healthy, dedicated blood donors, but because this study used a whole blood:citrate ratio of 8:1 rather than the usual 15:1, these symptoms were likely due to citrate toxicity. Furthermore, these symptoms resolved in all cases within 5 to 10 minutes after saline administration or a decrease in the plasma return rate, and there was no correlation between the occurrence of these symptoms and donor age or sex. Incidentally, the amount of 3-percent CP2D typically infused into the donor in the 2-unit RBC apheresis procedure is approximately 40 to 60 mL, much less than that infused in a typical plateletpheresis procedure (368-799 mL 2% ACD-A).[13] For example, in one study, an average of 55 ± 9 mL of 3 percent CP2D was infused to collect an absolute RBC volume of 407 ± 16 mL.[11]

Table 7. Symptoms reported with 2-unit RBC apheresis

Study	Number of procedures	Reactions		
		Severe	Moderate*	Mild†
Schmidt et al.[7]	64	0	0	10
Smith et al.[11]	9	0	0	7
Scott et al.[6]	566	0	6	148
Meyer et al.[4]	49	0	11	49

* "Moderate" not defined in article by Scott et al.[6] In Meyer et al.,[4] the reactions were chest tightness (8/11) and hypotension (3/11).

† "Mild" reactions included numbness, tingling, dizziness, lightheadedness, faintness, nausea, chills, and diaphoresis.

Physiologic signs of anemia with 2-unit RBC apheresis

As well as having no symptoms of anemia, donors receiving saline replacement appear to lack clinical signs of anemia or blood loss.[11,14,15] It is important to note, however, that subjects in these studies were healthy allogeneic blood donors without underlying medical problems. Smith et al.[11] randomly assigned 30 subjects recruited from previous blood donor studies and from a notice posted in the undergraduate gymnasium to sham, 206-mL, and 414-mL RBC apheresis with saline replacement. They found no significant difference between the three groups in blood pressure and pulse by ambulatory monitoring immediately after donation and for the rest of the day of donation.

Exercise capacity also does not appear to be significantly affected. In 30 donors with a mean age of 29 years who were randomly assigned in double-blind fashion to sham, 190-mL, and 380-mL RBC apheresis, there was no significant difference between treatment groups in maximal O_2 consumption (VO_2max) decrease, anaerobic threshold, maximum heart rate, respiratory exchange ratio, and maximum power at 0, 2, 7, and 14 days after donation.[14] The decline in VO_2 max from baseline was greatest on Day 2 (0.6%, 1.8%, and 8.2% in sham, 1-unit, and 2-unit groups, respectively), but the groups did not differ ($p = 0.28$). Sherman et al.[12] had similar results for VO_2 max in their study of eight experienced whole-blood donors (4 males, 4 females) with an age range of 21 to 38 years and an estimated RBC loss of 360 to 454 mL from 2-unit RBC apheresis. Even though the mean VO_2 max decreased 14 percent from baseline 24 hours after donation, seven of eight donors noted no difference in physical ability or work capacity compared to their experiences after standard whole-blood donation.

Risk of iron-deficiency anemia with 2-unit RBC apheresis

In regard to longer-term effects, allogeneic 2-unit RBC apheresis donors do not appear to be at greater risk for iron deficiency than whole-blood donors. Over a 1-year period, Meyer et al.[4] followed serum ferritin, serum iron, total iron-binding capacity, transferrin saturation, and zinc protopor-

phyrin/heme ratios in 40 donors divided between an RBC apheresis group donating 450 mL of RBCs every 4 months and a whole-blood group donating 225 mL of RBCs every 2 months. Half of the donors in each group received iron supplementation. No significant difference in any iron balance measurement was found between whole-blood and apheresis donors (see Fig. 1[4]) or between male and female donors. There was a significant increase in iron stores from the donor's baseline level in donors who received iron supplementation, while there was a decrease from baseline level in those who did not (see Fig. 3[4]), and three donors in the whole-blood group without iron supplementation developed unacceptably low Hct values and ferritin levels <12 ng per mL after donating 4, 1, and 4 units, respectively. Therefore, although no measures of iron balance became abnormally low in apheresis donors without iron supplementation, all regular 2-unit RBC apheresis donors should probably be given iron supplementation. The study by Sherman et al.[12] also supports this conclusion, as two of eight 2-unit apheresis donors, both female, without iron supplementation had ferritin levels <12 ng per mL at 16 weeks after donation (although one of these donors had a predonation serum iron level below the normal range).

Hematologic recovery from 2-unit RBC apheresis donation

Smith et al.[11] compared the hematopoietic response of allogeneic RBC apheresis donors of 206 mL versus 414 mL for 14 days after donation, and found that 2-unit RBC apheresis donors can appropriately compensate for the greater absolute RBC volume removed. Serum erythropoietin was significantly increased (approx. 10-12 U/L above baseline) in the 2-unit apheresis group over the level in the other two groups on Days 2 and 7. On Day 14, however, although still elevated approximately 5 U per L above baseline, this increase ceased to be significant (see Fig. 5[11]), which is not entirely surprising, given that, at 14 days after donation, the mean serum Hb of 2-unit apheresis donors (approx. 13.6 g/dL) was 90 percent of the baseline mean of 15.1 percent. The increase in serum Hb correlated with a mean increase in body Hb of 93 ± 28 g in 2-unit donors, compared to 73 ± 32 g in 1-unit donors. Smith et al. also looked at 2,3 DPG levels and found an increase only in the 2-unit donor group, which reached significance only at Day 14 (see their Fig. 6). The article suggests that this particular pattern of 2,3 DPG increase is more compatible with reticulocytosis than with intraerythrocytic 2,3 DPG synthesis.

An important issue in hematologic recovery after 2-unit RBC apheresis is the frequency of donation that is possible with 2-unit RBC apheresis. The FDA currently restricts the interval between 2-unit RBC apheresis procedures to 112 days. This interval appears safe: in the study by Meyer et al.,[4] in which predonation Hct levels of 41 percent for men and 38 percent for women were required, 20 of 20 apheresis donors (10 male, 10 female) were able to donate 450 mL of RBCs at 4-month intervals.

Of interest, however, especially in autologous donation, is whether this interval can be safely shortened. Sherman et al.,[12] selecting eight healthy donors (4 male, 4 female) whose Hct after apheresis and volume equilibration would not be <32 percent, found that, by 56 to 77 days after donation, all donors had a Hct of at least 38 percent. McNeil et al.,[16] using radiolabeled RBCs to measure RBC volume and a crossover study design with six donors (data on sex and health not provided), found no significant difference between blood volume 42 days after 2-unit RBC apheresis and 42 days after whole-blood donation. Smith et al.,[11] however, found that, despite iron supplementation in 2-unit RBC apheresis donors selected for a postdonation Hct >30 percent, five of five males, but only one of five females, had a Hct 14 days after donation that was high enough to allow repeat 2-unit donation. Evaluated together, these three studies suggest that, for donors without significant medical problems, the interval between 2-unit RBC apheresis procedures could perhaps be shortened to 6 weeks for both males and females, and to as little as 2 weeks for males only.

Functionality of RBCs collected by apheresis

Four studies show that, even after 42 days of storage, RBCs collected by apheresis are as functionally intact as those collected by traditional whole-blood donation, as measured by rates of hemolysis, ATP levels, and 24-hour percentage of in vivo recoveries (Table 8). RBC apheresis units collected by use of the diposable sets with attached CP2D and AS-3,[17] as well as those collected with the more recently developed dry disposable kits,[18] have been tested. In the study by Smith et al.,[15] even though the plasma potassium rose from 2.6 ± 0.3 on Day 0 to 48.7 ± 6.1 mEq per L on Day 42, the percentage of hemolysis in 0.44-percent saline was stable at 50 percent on both Days 0 and 42.

Conclusions

Although further study of safe-donor criteria in the autologous-donation setting is needed, 2-unit RBC apheresis as restricted by the current FDA guidelines does not seem to cause donor anemia in regard to symptoms, signs, or iron

Table 8. Characteristics of 2-unit RBC apheresis units after 42 days of storage

Study	Plasma potassium (mEq/L)	Percentage of hemolysis	ATP levels (μmol/g Hb)	Percentage of 24 hour recovery
Smith et al.[15]	48.7± 6.1	*	81% of Day 0	
Holme et al.[17]		0.50 ± 0.33		78 ± 5
Whitley et al.[18]		0.40 ± 0.2	3.1 ± 0.5	83 ± 5

* Fifty percent hemolysis at 0.44-percent saline; no change from initial value.

deficiency, as long as iron supplementation is administered. In regard to recipients, apheresis RBC units have in vitro and in vivo qualities similar to those of manually collected RBC units. Therefore, risk associated with 2-unit RBC apheresis appears to be minimal.

What are the potential benefits of 2-unit RBC apheresis over traditional whole-blood donation? For both allogeneic and autologous donors, one benefit is the potential to give an equivalent number of RBC units as in traditional whole-blood donation, but with less frequent visits to the blood center. In the study by Meyer et al.,[4] for example, an absolute RBC volume donation of 1350 mL over a 1-year period required six visits for whole-blood donors but only three visits for apheresis donors. Because there is a significant increase in erythropoietin, lasting at least 7 to 14 days, with simultaneous 2-unit RBC donation over that seen with 1-unit RBC donation,[11] a theoretical benefit to surgical patients donating autologous blood who undergo 2-unit RBC apheresis 7 to 14 days preoperatively may be a more rapid postoperative reticulocytosis, which would prevent possible anemia requiring allogeneic transfusion in addition to the use of the autologous units.

For the recipient, one benefit can be decreased donor exposure, if the transfusion service develops systems to allocate both units to the same patient. Another benefit is that the expected rise in Hb or Hct after transfusion should be more predictable, because RBC apheresis units contain a defined amount of RBCs per unit, rather than the variable amount in whole-blood units. Finally, because anticoagulant is metered at a defined rate in proportion to whole-blood withdrawal, apheresis avoids the theoretical "lesion of collection" that may occur in traditional whole-blood collection, in which the first RBCs collected are exposed to a higher concentration of anticoagulant and may therefore be prematurely destroyed.[19]

For the blood center, one advantage is the potential to custom-tailor component collection to inventory needs, such as those for D– RBCs or phenotypically matched RBCs for chronically transfused patients. One could envision a system in which group O donors are targeted for RBC apheresis and group AB donors for plasmapheresis.

Optimizing RBC collection becomes especially important with a dwindling donor base[20] and difficult donor recruitment. Beeler et al.[21] published a theoretical analysis of the effect of converting 25 percent and 50 percent of whole-blood collections to RBC apheresis collections (in which 50% of the RBC apheresis procedures are 2-unit RBC collections, and 50% are 1-unit RBC and 1-unit fresh-frozen plasma collections). They found that the number of donors needed to produce the necessary number of blood components decreased by 11 percent and 20 percent in the 25-percent and 50-percent conversions, respectively (Table 9).

Finally, conversion to RBC apheresis may save money by decreasing the amount of component processing, technical preparation time, quality control, paperwork, and testing (to one set of laboratory tests/2 units). Beeler et al.[21] estimated that conversion of 50 percent of whole-blood collections to RBC apheresis would result in a 68-percent decrease in component preparation, a 21-percent decrease in component labeling, and a 21-percent decrease in the number of donor test profiles required. RBC apheresis may also become more cost-effective, given the current trend against the use of random-donor platelets, the fees for which often subsidize the cost of RBC units prepared from whole blood. Even if partial conversion to RBC apheresis is not more economical than the current status quo, its benefit to recipients may justify fee increases to the patient. As RBC apheresis technology advances, further study of its economic impact, the marketplace issues, and clinical experience with its components will determine its future role in transfusion medicine.

Table 9. Predicted effect of converting 25 and 50 percent of whole-blood collections to 2-unit RBC apheresis procedures

	RBC apheresis		
	0%	25%	50%
Total number of donors	128,926	114,367	102,549
Total apheresis donors	12,455	41,573	73,432
Whole-blood donors	116,471	72,794	29,118
Whole-blood platelets	42,651	42,651	26,206
Whole-blood FFP	33,516	4,398	0
Cryoprecipitate	6,094	6,094	6,094
Recovered plasma	76,861	62,302	47,743
2-unit RBC apheresis (RBCs)	0	29,118	58,236
RBC and plasma apheresis collection			
RBCs	0	14,559	29,118
FFP	0	14,559	29,118
Plateletpheresis	12,455	12,455	15,196
Number of components to label	288,048	256,731	228,468
Number of components to process	275,595	194,334	90,535

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